Report on the Investigation Results

November 25, 2016
Pharmaceuticals and Medical Devices Agency

I. Overview of Product

[Non-proprietary name]

(1) milnacipran hydrochloride (2) duloxetine hydrochloride (3) venlafaxine hydrochloride

[Brand name]

(1) Toledomin Tablet 12.5 mg, Toledomin Tablet 15 mg, Toledomin Tablet 25 mg, Toledomin Tablet 50 mg, etc.
(2) Cymbalta Capsule 20 mg, Cymbalta Capsule 30 mg
(3) Effexor SR Capsule 37.5 mg, Effexor SR Capsule 75 mg

[Approval holder]

(1) Asahi Kasei Pharma Corporation and others (2) Shionogi & Co., Ltd. (3) Pfizer Japan Inc.

[Indications]

(1) (2) (3) Depression/depressed state
(2) Pain accompanying the following diseases
Diabetic neuropathy, fibromyalgia, chronic lumbago

[Dosage and administration]

(1) Usually, for adults, milnacipran hydrochloride should be administered orally in two to three divided doses after meals, at an initial dose of 25 mg per day, with the dose gradually increased to 100 mg per day. The dose should be increased or decreased as appropriate depending on the patient's age and symptoms.

For elderly patients, milnacipran hydrochloride should be administered orally in two to three divided doses after meals, at an initial dose of 25 mg per day, with the dose gradually increased to 60 mg per day.

(2) 1. Depression/depressed state, pain accompanying diabetic neuropathy

Usually, for adults, duloxetine hydrochloride should be administered orally once per day after breakfast at a dose of 40 mg. Administration should be started at 20 mg per day, and the daily dose should be increased in steps of 20 mg, at intervals of at least one week. If the drug effect is incomplete, the dose may be increased up to 60 mg per day.

2. Pain accompanying fibromyalgia and pain accompanying chronic lumbago

Usually, for adults, duloxetine hydrochloride should be administered orally once per day after breakfast at a dose of 60 mg. Administration should be started at 20 mg per day, and the daily dose should be increased in steps of 20 mg, at intervals of at least one week.

(3) Usually, for adults, venlafaxine hydrochloride should be administered orally once per day after meals at an initial dose of 37.5 mg, increased to 75 mg after one week. The dose should be increased or decreased as appropriate depending on the patient's age and symptoms, but to no more than 225 mg per day, with increases in the daily dose in steps of 75 mg at intervals of at least one week.

[Investigating office] Office of Safety II

II. Background of the Investigation

1. Status in Japan

Milnacipran hydrochloride (milnacipran), duloxetine hydrochloride (duloxetine), and venlafaxine hydrochloride (venlafaxine) are serotonin-noradrenaline reuptake inhibitors (SNRIs). Milnacipran was approved for the indication "depression/depressed state" in September 1999, followed by approvals for duloxetine in January 2010 and venlafaxine in September 2015 for the same indication. Duloxetine has additionally been approved for "pain accompanying diabetic neuropathy (approved in February 2012)," "pain accompanying fibromyalgia (approved in May 2015)," and "pain accompanying chronic lumbago (approved in March 2016)."

The “Important Precautions” section for SNRIs contained the following precaution prohibiting driving or operating other machinery. Milnacipran, the first SNRI, was approved based on the incidence of adverse drug reactions in Japanese clinical studies and precautions in Japanese package insert of tricyclic and tetracyclic antidepressants that were already approved contained “as symptoms such as somnolence and dizziness may occur, caution patients not to engage in hazardous machine operation, such as driving a car, during the treatment.” Duloxetine and venlafaxine, which were subsequently approved, contained the same precaution in the “Important Precautions” section, based on the precautions for the already approved SNRI milnacipran.

The “Important Precautions” sections for selective serotonin reuptake inhibitors (SSRIs), which are similar drugs, state that “as symptoms such as somnolence and dizziness may occur, caution patients about operating hazardous machine such as driving a car,” and thus driving and the operation of other potentially hazardous machinery is not prohibited, with the exception of fluvoxamine maleate (fluvoxamine), whose package insert lists “consciousness disturbance such as depressed level of consciousness and loss of consciousness” in the “Clinically Significant Adverse Reactions” section.

In January 2014, a “Request Regarding Package Inserts” about precautions relating to driving and the like was submitted to the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (the Safety Division) by the Japanese Society of Neuropsychopharmacology and Japanese Society of Mood Disorders. The request stated that for almost all psychiatric patients, continuing treatment with psychotropics is essential to improve symptoms and prevent recurrence, but that Japanese package inserts for all psychotropics except for three antidepressants (paroxetine hydrochloride hydrate, sertraline hydrochloride, and escitalopram oxalate) require that patients be told to stop driving, with the result that not only does a treatment that should be a benefit deprive patients of their normal lifestyle, but patients are unable to receive the treatment they need, risking an increase in the number of patients who experience aggravation of symptoms or recurrence, and therefore it was requested that the package inserts be revised. In view of this request, on September 6, 2016, the Safety Division requested that the Pharmaceuticals and Medical Devices Agency (PMDA) conduct an investigation into the safety of SNRIs when driving or operating other hazardous machinery, and in response to this request, PMDA investigated the

safety of SNRIs when driving or operating other hazardous machinery.

PMDA held an Expert Discussions in this investigation. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product, in accordance with the provisions of "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

2. Status in other countries

We have checked the contents of SNRI package inserts in Europe and the US relating to precautions on driving and operation other hazardous machinery. None of the package inserts uniformly prohibits driving. They state that a decision should be made based on the patient's condition.

The final report of the Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) Project[1] conducted in Europe in 2006 through 2011, contains the precaution that patients treated with duloxetine and venlafaxine should avoid driving, since these drugs have adverse drug reactions that, although all non-severe, affect the central nervous system, and thus somnolence and dizziness can easily occur in the initial stages of treatment.

III. Investigation by PMDA

1. Accumulated adverse drug reaction reports in Japan

The marketing authorization holders for the SNRIs provided the numbers of adverse drug reaction reports for 21 events[2] that may affect driving or are related to accidents (driving-related events) obtained in Japan from launch until May 31, 2016, and gave the following explanations.

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[1] Trinidad Gómez-Talegón, et al., Classification of medicinal drugs and driving: Co-ordination and synthesis report, in Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) 6th Framework Programme, Deliverable D.4.4.1, 1-243 (2011).

[2] Events corresponding to the MedDRA PTs "depressed level of consciousness," "loss of consciousness," "altered state of consciousness," "mental impairment," "stupor," "syncope," "sudden onset of sleep," "somnolence," "hypersomnia," "lethargy," "vertigo,", "dizziness postural," "dizziness," "disturbance in attention," "amnesia," "amnestic disorder," "transient global amnesia," "retrograde amnesia," "memory impairment," "accident," and "road traffic accident"

1.1 Milnacipran

For the originally marketed product, Toledomin, reports of 383 events in 359 patients (of which 6 events in 6 patients were serious) have been accumulated. The observed adverse drug reactions (Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs)) were “dizziness” (164 events in 142 patients), “somnolence” (138 events in 137 patients), “dizziness postural” (55 events in 54 patients), “loss of consciousness” (7 events in 7 patients), “depressed level of consciousness” (5 events in 5 patients), “amnesia” and “memory impairment” (3 events in 3 patients for each PT), “altered state of consciousness” and “mental impairment” (2 events in 2 patients for each PT), and “stupor,” “syncope,” “hypersomnia,” and “disturbance in attention” (1 event in 1 patient for each PT).

The incidences of adverse drug reactions were relatively higher in the initial stages of administration, with the most common onset times being in the period from Day 1 to 7 of administration (145 events), followed by the period from Day 8 to 14 (68 events), and then Day 15 to 21 (53 events). Adverse events that were common in the initial stages of administration were “dizziness,” “somnolence,” and “dizziness postural.” Of the events related to consciousness disturbance[3] (a total of 16 events in 16 patients), 4 serious cases were reported, and while 2 of these events were likely to be due to the effects of concomitant drugs (hypnotics (3 events), H_2 receptor antagonists (1 event), and hypotensives (2 events) (including overlapping cases and cases where multiple drugs of the same category were coadministered), and details of the other cases were unknown. There were no reports of the adverse drug reactions “road traffic accident” or “accident,” but it was found that “loss of consciousness” (in 2 patients) and “altered state of consciousness” (in 1 patient) led to accidents while driving. In these cases, the periods from day 1 of administration of Toledomin until onset were unknown, 10 months, and 31 months, respectively. In the case that occurred after 31 months, the patient recovered from the altered state of consciousness while taking Toledomin, but in the other cases, there were insufficient details.

Adverse reactions reported with generic drugs were “dizziness” (3 events in 2 patients)

[3] Events corresponding to the MedDRA PTs “depressed level of consciousness,” “loss of consciousness,” “altered state of consciousness,” “stupor,” and “syncope”

and “dizziness postural” (2 events in 2 patients). The onset time of adverse reactions was between Day 1 to 7 of administration for 1 patient but was unknown for others.

1.2 Duloxetine

For duloxetine, reports of 1493 events in 1479 patients (of which 47 events in 41 patients were serious) have been accumulated. The observed adverse drug reactions were “somnolence” (915 events in 913 patients), “dizziness” (449 events in 440 patients), “dizziness postural” (30 events in 29 patients), “loss of consciousness” (18 events in 18 patients), “syncope” (19 events in 17 patients), “altered state of consciousness” (13 events in 13 patients), “memory impairment” (10 events in 10 patients), “amnesia” and “vertigo” (8 events in 8 patients for each PT), “depressed level of consciousness” (6 events in 6 patients), “disturbance in attention” and “road traffic accident” (5 events in 5 patients for each PT), “hypersomnia” (4 events in 4 patients), “mental impairment,” “stupor,” and “lethargy” (1 event in 1 patient for each PT).

The incidences of adverse drug reactions were relatively higher in the initial stages of administration, with the most common onset times being in the period from Day 1 to 7 of administration (448 events), followed by the period from Day 8 to 14 (64 events), and then Day 15 to 21 (36 events). Adverse events that were common in the initial stages of administration were “somnolence” and “dizziness.” Of the events related to consciousness disturbance (a total of 57 events in 55 patients), 16 events occurred within the first week after the start of administration, with no more than 4 events per week occurring from week 2 onwards, and a total of 12 events in week 9 or later. Of the 55 cases related to consciousness disturbance, information on 43 events was obtained, and these involved concomitant administration with other noradrenergic and specific serotonergic antidepressants/SSRIs/SNRIs (9 events), central nervous system agents such as benzodiazepines (28 events), antiepileptics (3 events), pregabalin (9 events), hypotensives (7 events), or insulin (3 events) (including overlapping cases and cases where multiple drugs of the same category were coadministered), and in addition, some patients were found to have factors such as a history of convulsion (1 event), concurrent conditions such as electroencephalogram abnormal/organic brain abnormal (1 event each) and hypoglycaemia (2 events), or overdose (3 events), or the like, and there were no cases out of the 55 patients with events related to consciousness disturbance where

duloxetine was obviously involved.

Of the 5 cases of road traffic accidents in Japan (of which 2 cases were serious), the serious cases both involved patients on multi-drug therapy, and the accidents occurred 11 days and at least 2 years, respectively, after the start of administration, and judgement impaired and loss of consciousness (somnolence) were reported. Details of the other 3 non-serious cases are unknown.

1.3 Venlafaxine

For venlafaxine, reports of 201 events in 197 patients (of which 3 events in 3 patients were serious) have been accumulated. The observed adverse drug reactions were “somnolence” (145 events in 145 patients), “dizziness” (45 events in 45 patients), “memory impairment,” “hypersomnia,” “amnesia,” and “dizziness postural” (2 events in 2 patients for each PT), and “loss of consciousness,” “road traffic accident,” and “disturbance in attention” (1 event in 1 patient for each PT).

The incidences of adverse drug reactions were relatively higher in the initial stages of administration, with the most common onset times being in the period from Day 1 to 7 of administration (28 events), followed by the period from Day 8 to 14 (16 events), and then Day 15 to 21 (5 events). Adverse events that were common in the initial stages of administration were “somnolence” and “dizziness.” Of the events related to consciousness disturbance, the only serious case reported was 1 case of “loss of consciousness” and in this case, a causal relationship with venlafaxine could not be ruled out, but there was insufficient information.

The 1 case of a road traffic accident in Japan was a case where the road traffic accident was likely caused by the patient experiencing sleep loss due to nocturnal awakening after being administered venlafaxine and falling asleep while driving the next day.

2. Accumulated overseas adverse drug reaction reports relating to road traffic accidents

The marketing authorization holders for the SNRIs gave the following explanation of the overseas adverse event reports obtained overseas relating to road traffic accidents[4] (and serious cases) between the launch of the pharmaceutical and May 31, 2016.

[4] Events corresponding to the MedDRA PTs “road traffic accident” and “accident”

2.1 Milnacipran

Based on data obtained from overseas partners dealing in the original marketed product, 11 cases of road traffic accidents relating to milnacipran were found. Of these, in 2 cases, the “loss of consciousness” and “disorientation” considered likely to be the cause of the road traffic accident occurred 3 days and 9 days respectively after the start of administration of milnacipran. For the other 9 cases, there was no information about the adverse events, and they were cases that involved concomitant administration of multiple pharmaceuticals and cases with insufficient detailed information.

2.2 Duloxetine

Based on data obtained from overseas partners dealing in duloxetine, 29 cases of road traffic accidents relating to duloxetine were found. Of these, in 15 cases, there was insufficient detailed information, and in the other cases, the event occurred during the administration of duloxetine, but multiple other drugs acting on the central nervous system were concomitantly administered.

2.3 Venlafaxine

For venlafaxine, 7 cases of road traffic accidents were found. Of these, 2 cases occurred 8 days and 13 days, respectively, after the start of administration; but for the other 5 cases, detailed information about what led to the road traffic accident or accident was unknown.

3. Clinical studies that assessed the effect of SNRIs on driving

3.1 Milnacipran

***Int J Psychiatry Clin Pract* 2004; 8: 109-115**[5]

A placebo-controlled, double-blind crossover study of milnacipran in healthy adults was conducted in France (4 subjects in each of the milnacipran 100 mg/day group and placebo group). There was no significant difference between the milnacipran 100

[5] Richet F et al, Effects of milnacipran on driving vigilance. *Int J Psychiatry Clin Pract* 2004; 8: 109-115

mg/day group and placebo group in motor response to auditory and visual stimulation and equilibrium on a sensory platform, and no obvious effect from milnacipran was observed in a real driving situation.

3.2 Duloxetine

***Poster presentation in the 49th Annual NCDEU meeting*, 2009[6]**

Clinical research in the US investigated "the effect on driving performance in a driving simulator in patients with depression before and after treatment with duloxetine" (sample size: 12 subjects). When patients with depression were administered 60 mg of duloxetine and then underwent measurement of their electroencephalogram (EEG), gamma waves, which, it has been suggested, reflects cognitive processing and performance, and alpha waves, known to be associated with drowsiness/wakefulness, were measured, there was no significant difference from historical normal. Scenario analysis from a driving simulator did not find significant difference in driving performance before and after treatment with duloxetine.

3.3 Venlafaxine

***J Clin Psychopharmacol* 1998; 18: 212-221[7]**

To investigate venlafaxine's effects on driving performance, a 4-period (15 days per period), placebo-controlled (placebo, venlafaxine 75 mg/day, venlafaxine 150 mg/day, and mianserin hydrochloride (mianserin) 60 mg/day), randomized, double-blind crossover study in healthy adults was conducted in the Netherlands (sample size: 37 subjects). In the group administered the tetracyclic antidepressant mianserin at 60 mg/day, the Standard Deviation of Lateral Position (SDLP), which indicates the extent of horizontal swaying while driving, was significantly higher than in the placebo group, and psychomotor performance decreased significantly, while in the venlafaxine groups, there was not significant effect on the primary endpoint SDLP compared to the placebo

[6] Bastani B et al, Measurement of Alertness in Patients with Major Depression Before and After Treatment with Duloxetine: Evaluation of Treatment Effect on Performance in Driving Simulator, *Poster presentation in the 49th Annual NCDEU meeting*, 2009

[7] O'Hanlon J F et al, Venlafaxine's Effects on Healthy Volunteers' Driving Psychomotor and Vigilance Performance During 15-day Fixed and Incremental Dosing Regimens, *J Clin Psychopharmacol* 1998; 18: 212-221

group, and there was almost no effect on psychomotor performance.

***Pharmacopsychiatry* 2015; 48: 65-71**[8]

A randomized case control study in depression patients was conducted in Germany. Depression patients (20 subjects) were administered venlafaxine for 28 days, and it is reported that depression symptoms and psychomotor functions improved compared to before administration, and their global driving ability scores significantly improved. The driving ability of patients who became able to make outpatient visits due to venlafaxine treatment was assessed using a global rating assessed by an instructor in the subject's vehicle actually driving along normal roads for 50 minutes, and no difference in driving ability compared with healthy adults was found.

4. Comparison between SNRIs and similar drugs

***Neuropsychiatr Dis Treat* 2013; 9: 555-565**[9]

In a double-blind, comparative study of milnacipran and the SSRI paroxetine hydrochloride hydrate (paroxetine) in Japanese major depression patients (904 safety evaluation subjects, 75 sites), the incidences of adverse drug reactions in the milnacipran 100 mg/day group and 200 mg/day group were 71.6% and 68.8%, respectively, which were similar to the incidence in the paroxetine 30 mg/day and 40 mg/day groups of 69.3%, and no significant difference was found, and no major difference was found in the incidences of the driving-related events "dizziness," "dizziness postural," and "somnolence."

Japanese clinical trial (the 16A203C study)[10]

A Japanese multicenter, double-blind, parallel-group, comparative study in patients with depression and depressed state (total subjects receiving treatment: 495 subjects, duloxetine 40 mg/day group: 91 subjects, duloxetine 60 mg/day group: 84 subjects, placebo group: 156 subjects, paroxetine group: 164 subjects) to investigate the

[8] Brunnauer A et al, Driving Performance and Psychomotor Function in Depressed Patients Treated with Agomelatine or Venlafaxine, *Pharmacopsychiatry* 2015; 48: 65-71
[9] Kamijima K et al, Double-blind, comparative study of milnacipran and paroxetine in Japanese patients with major depression, *Neuropsychiatr Dis Treat* 2013; 9: 555-565
[10] Cymbalta application materials 2.7.6.5.2

superiority of the combined duloxetine 40 mg/day and 60 mg/day group to the placebo group and non-inferiority to the paroxetine 20 to 40 mg/day group (the paroxetine group) was conducted. In safety results, the driving related events that occurred in the duloxetine 40 mg/day and 60 mg/day groups and paroxetine group were “somnolence” (20 subjects in the 40 mg/day group, 17 subjects in the 60 mg/day group, and 36 subjects in the paroxetine group; the same order is used below), “dizziness” (10 subjects, 4 subjects, 9 subjects), “dizziness postural” (6 subjects, 1 subject, 6 subjects), “vertigo” (3 subjects, 1 subject, 4 subjects), and in addition to these adverse drug reactions, in the paroxetine group, “mental impairment” in 1 subject and “syncope” in 1 subject occurred. The types of adverse drug reactions were similar between the duloxetine 40 mg/day group, duloxetine 60 mg/day group, and paroxetine group. None of the events that occurred were serious adverse drug reactions. The adverse drug reaction with the highest incidence in each group was “somnolence,” which occurred within 4 weeks of the start of administration, with the exception of 1 case in the duloxetine 60 mg/day group. “Vertigo,” “dizziness,” and “dizziness postural” occurred more than 6 weeks later, but their incidences in the duloxetine 40 mg/day group, 60 mg/day group, and paroxetine group were similar, and overall, the number of adverse drug reactions per observation week gradually decreased.

Overseas clinical trial (the F1J-US-HMCR (a) study)[11]

A multicenter, randomized, double-blind, parallel-group, placebo and active drug controlled comparative study of a group administered duloxetine at 60 mg/day in major depression with a group administered the SSRI escitalopram oxalate (escitalopram) at 10 mg/day as a control was conducted in the US (total number of subjects: 684 subjects, duloxetine 60 mg/day group: 273 subjects, escitalopram 10 mg/day group: 274 subjects, placebo group: 137 subjects). Of the 21 driving-related events reported, there were 9 events that occurred in active drug groups in the acute treatment phase and continued treatment phase, “dizziness” (34 subjects in the 60 mg/day group, 32 subjects in the escitalopram 10 mg/day group; the same order is used below), “somnolence” (20 subjects, 20 subjects), “disturbance in attention” (5 subjects, 5 subjects), “hypersomnia” (5 subjects, 1 subject), “memory impairment” (4 subjects, 1 subject), “lethargy” (3

[11] Cymbalta initial application materials 2.7.6.5.12

subjects, 3 subjects), “vertigo” (1 subject, 2 subjects), “syncope” (0 subjects, 2 subjects), and “dizziness postural” (0 subjects, 1 subject). There were no events that occurred with a significantly higher incidence in the duloxetine 60 mg/day group than in the escitalopram 10 mg/day group, and there were no serious driving-related events. The results of this study showed that there were no major differences in the types and incidences of adverse events between the duloxetine 60 mg/day group and escitalopram 10 mg/day group.

Overseas clinical trial (the F1J-MC-HMCQ study)[12]

A multicenter, randomized, double-blind, parallel-group, active-control, comparative study of a duloxetine 60 mg/day group, 90 mg/day group, and 120 mg/day group in major depression compared with groups administered the SNRI venlafaxine (a venlafaxine 75 mg/day group, 150 mg/day group, and 225 mg/day group) as controls was conducted in North America (total number of subjects: 504 subjects, duloxetine 60 mg/day group: 164 subjects, venlafaxine 75 mg/day group: 169 subjects, venlafaxine 150 mg/day group: 171 subjects). In this study, out of the 21 driving-related events, there were 10 events that occurred in the combined period containing the fixed dose phase and the dose titration phase, “dizziness” (30 subjects in the duloxetine 60 mg/day group, 26 subjects in the venlafaxine 75 mg/day group, and 26 subjects in the venlafaxine 150 mg/day group; the same order is used below) “somnolence” (24 subjects, 18 subjects, 13 subjects), “lethargy” (3 subjects, 2 subjects, 4 subjects), “disturbance in attention” (2 subjects, 3 subjects, 1 subject), “vertigo” (1 subject, 0 subjects, 0 subjects), “syncope” (1 subject, 0 subjects, 0 subjects) “hypersomnia” (0 subjects, 3 subjects, 3 subjects), “mental impairment (0 subjects, 2 subjects, 1 subject), “memory impairment” (0 subjects, 1 subject, 0 subjects), and “amnesia” (0 subjects, 0 subjects, 1 subject). The incidences of all events were similar between the venlafaxine groups and duloxetine groups, and there were no serious driving-related events.

***J Clin Psychopharmacol* 1998; 18: 212-221**[13]

[12] Cymbalta initial application materials 2.7.6.5.14
[13] O’Hanlon J F et al, Venlafaxine's Effects on Healthy Volunteers' Driving Psychomotor and Vigilance Performance During 15-day Fixed and Incremental Dosing Regimens, *J Clin Psychopharmacol* 1998; 18: 212-221

To investigate venlafaxine's effects on driving performance, a 4-period (15 days per period), placebo-controlled (placebo, venlafaxine 75 mg/day, venlafaxine 150 mg/day, and mianserin 60 mg/day), randomized, double-blind crossover study in healthy adults was conducted in the Netherlands (sample size: 37 subjects). In the venlafaxine 75 mg/day and 150 mg/day group, there was no significant effect on the primary endpoint SDLP compared to placebo, but in the group administered the tetracyclic antidepressant mianserin at 60 mg/day, driving performance and psychomotor skills decreased significantly compared with the placebo group.

***Eur Neuropsychopharmacol* 2014; 24: 1463-1474**[14]

The relationships between the binding affinity of antidepressants to various receptors and the incidences of adverse drug reactions observed in clinical studies were analyzed using multivariate analysis, and the relationship between 10 types of adverse drug reaction determined to be predictable, including "dizziness," "sedation," and "sleepiness," and the affinity with 24 types of transporter or receptor was reported.

The inhibition constant (Ki) showing the binding affinity with a serotonin transporter (5-HTT) suggested to have a negative correlation with sedation and sleepiness was approximately 1 nM for duloxetine and approximately 60 to 100 nM for milnacipran and venlafaxine. For SSRIs, the Ki of escitalopram for 5-HTT was approximately 2 nM, the Ki of paroxetine was approximately 0.3 nM, and the Ki of sertraline hydrochloride (sertraline) was approximately 1 nM.

The results for receptors were that the Ki of duloxetine for serotonin 5-HT_{2A}, which it has been suggested is related to dizziness, sedation, and sleepiness, for 5-HT_{2C}, which it has been suggested is related to dizziness and sleepiness, and for 5-HT_6, which it has been suggested is related to sleepiness, were 1 μM or lower. There were no receptors for which the Ki of milnacipran or venlafaxine was 1 μM or lower.

The results for SSRIs were that the Ki of escitalopram for adrenaline α 1, which it has been suggested is related to dizziness, sedation, and sleepiness, was 1 μM or higher. The Ki of paroxetine for muscarine M_2, M_3, M_4, and M_5 receptors, which it has been

[14] Michl J et al, A multivariate approach linking reported side effects of clinical antidepressant and antipsychotic trials to in vitro binding affinities, *Eur Neuropsychopharmacol* 2014; 24: 1463-1474

suggested are related to dizziness, was 1 μM or lower, and the Ki of sertraline for adrenaline α 1 was 1 μM or lower.

The selectivity of each drug is different, but duloxetine and many SSRIs show high affinity for 5-HTT, which it has been suggested has a negative correlation with sedation and sleepiness, and their Ki values for all receptors suggested to be related to dizziness, sedation, and sleepiness were 1 μM or lower.

Milnacipran and venlafaxine had somewhat low affinity for 5-HTT, and there were no available data for other receptors of milnacipran, but for venlafaxine, there were no receptors showing a Ki of 1 μM or lower.

5. Summary of investigation at PMDA

At the time each SNRI was approved, a precaution prohibiting driving or the operation of other machinery was provided, following the example oftricyclic and tetracyclic antidepressants and already approved SNRIs. However, the precautionary notices for SSRIs other than fluvoxamine do not prohibit driving or the operation of other machinery.

According to the result of clinical studies, it was not suggested that the SNRIs in this investigation reduced driving performance relative to administration of placebo or when not administered (see the section “3. Clinical studies that assessed the effect of SNRIs on driving”). Comparison of their safety profiles with SSRIs did not show a greater number of accumulated reports of adverse drug reactions that could affect driving, and pharmacologically, no major differences in affinity to receptors relating to “dizziness,” “sedation,” or “sleepiness” were found (see the section “4. Comparison between SNRIs and similar drugs”).

Accordingly, PMDA considers that it is scientifically reasonable to change the precautions for SNRIs on driving or operating other machinery in line with the precautions for SSRIs to allow flexible handling depending on the patient’s situation, rather than uniform prohibition. At present, the package inserts for all SNRIs approved in Japan contain precautions prohibiting driving, and therefore PMDA considers that aligning the precautions for SNRIs relating to driving or operating other machinery with the precautions for SSRIs will broaden treatment options and provide proper treatment to patients, and that this proper treatment will contribute to preventing the aggravation of

symptoms and recurrences.

On the other hand, there have been no small number of reports of adverse drug reactions that may affect driving, such as dizziness or somnolence, although many of these cases are non-serious. Although there are no cases where the involvement of SNRI is clearly present, there have been reports of consciousness disturbance related events that may affect driving without patients themselves noticing signs of the event (see the section “1. Accumulated adverse drug reaction reports in Japan”). The possible influence of concomitant medication or the patient’s condition could not be ruled out for any of the consciousness disturbance related events for SNRIs reported in Japanese post-marketing reports, and there were no cases of road traffic accidents in Japan with an obvious relationship between the consciousness disturbance related event and the SNRI. Moreover, taking into account the current situation in overseas countries, where driving is not uniformly prohibited but there are not many accumulated reports of accidents during treatment with SNRIs, PMDA considers that it is possible to revise the precautions so that they are similar to those for SSRIs in Japan or SNRIs overseas and do not uniformly prohibit driving. However, the risk of accidents due to events such as dizziness, somnolence, or consciousness disturbance are posed not only on the patients themselves but also on third parties. Accordingly, when the precautions on patients receiving SNRIs driving or operating other machinery are revised, the prescribing physician and healthcare providers must observe the patient’s condition carefully, and alert the patient to ensure that the necessary care is taken while driving and that the patient does not drive if he or she experiences adverse drug reactions such as dizziness or somnolence. We consider that depending on the patient’s background (for example, the condition of the psychiatric illness, complications, or concomitant medications), there are still cases where patients receiving SNRIs should not drive or operate other machinery, but there are limitations to investigating in detail the specific cases in which driving is possible and listing them as precautions on the package inserts. We consider that it is important for relevant academic societies and the marketing authorization holders to provide the necessary information so that the prescribing physician can make the proper decision about whether or not it is appropriate for the patient to drive and give instructions to the patient in actual clinical practice.

The precautions for SSRIs on driving state that in the case of paroxetine only, symptoms such as dizziness are often observed in the early stages of treatment. For the SNRIs in this investigation, adverse drug reactions such as somnolence and dizziness tend to occur at an early stage after the start of administration, but it is unknown whether this is the time when administration is started or the time of switching over from another drug, and the possibility of an influence from the condition of the patient when administration is started cannot be ruled out. Therefore, PMDA considers that SNRIs may not always cause many adverse drug reactions in the initial stage of administration, as paroxetine does. However, PMDA wanted to discuss with expert advisors about the need to observe the effect of the drug for a fixed period before making a decision about whether it is appropriate for the patient to drive.

PMDA discussed the appropriateness of the above-mentioned view of PMDA at an Expert Discussion.

As a result, expert advisors expressed their opinions that the frequency and severity of dizziness or somnolence, etc., with SNRIs do not significantly differ from those with SSRIs considering the clinical experiences etc., or that “Important Precautions” of SNRIs are not consistent with SSRIs, similar drugs to SNRIs. Consequently, revision of package inserts of SNRIs in line with SSRIs was supported by expert advisors to allow flexibility in the precautions regarding the operation of machinery, including driving, rather than uniform prohibition to address the individual situation of patients.

Expert Discussion discussed the necessity in the package inserts for a fixed period of observation for effects of the drug before deciding the appropriateness of driving. Some of the expert advisors maintained that it is irrelevant to uniformly prohibit driving limited to a defined period of time following the start of administration because somnolence or dizziness tend to emerge when the dose is increased as well as when administration is started or be influenced by concomitant drugs while the actual driving skill is affected by the severity of depression of the patient. Consequently, expert advisors present unanimously agreed that it is not necessary to include in the package inserts a fixed period of observation for effects of the drug before deciding the appropriateness of driving.

There was also an opinion by an expert advisor regarding ensuring the precaution to

discourage patients from driving when aware of adverse reactions such as dizziness or somnolence, that such precautions are not necessary in the package inserts because there is no substantial difference between SSRI and SNRI, and their effects on driving can be assumed virtually equivalent, adding that US package inserts do not contain such precautions. PMDA explained to the expert advisor that it is important for physicians to instruct patients not to drive when they are aware of dizziness or somnolence, which actually emerge while receiving SNRI whether at the start of administration or not, and that it is appropriate to include the precaution to the effect, considering the European package inserts for duloxetine that contain such precautions. The expert advisor supported PMDA's opinion.

Other opinions from expert advisors regarding the revision this time were; that the revision will allow candid discussions over right or wrong of driving between physicians and patients focusing on conditions of individual patients; that it is important to explain the general onset tendency of adverse reactions of SNRIs that somnolence and dizziness are frequently observed often at an early stage of administration, i.e., until Day 7 of treatment; that preparation and distribution of brochures for patients as well as for physicians is necessary to ensure their understanding of adverse reactions of SNRIs.

Given the above, PMDA concludes as follows;

It is appropriate to revise the precautions for driving to the description similar to the precautions of SSRI, rather than the uniform prohibition of operating hazardous machinery including driving while receiving SNRI. However, there is a patient population who should not engage in driving due to the conditions of their psychiatric disorders or concomitant drugs etc. Therefore, patients who want to drive can be properly informed by physicians of the onset of adverse reactions to SNRIs that may affect driving and cautioned not to engage in driving when they become aware of somnolence and dizziness.

Additionally, in communicating the contents of precautions to be revised, healthcare providers should be fully informed by marketing authorization holders of the necessity for considering the status of control of psychiatric disorders in individual patients, frequency and tendency of adverse reactions such as instability of conditions,

somnolence or dizziness frequently perceived when administration is started or dose is increased. After the revision of package inserts, it will be important that clinical practices where patients are cared for be provided with prompt information by relevant academic societies and marketing authorization holders.

IV. Overall evaluation

PMDA has decided that it is appropriate to revise the precautions on the package insert as follows.

[Draft revision] Milnacipran

Add the underlined text and delete the strike-through text

Current version	Draft revision
2. Important Precautions (5) As symptoms such as somnolence and dizziness may occur, caution patients ~~not to engage in~~ hazardous machine ~~operation~~ such as driving a car ~~during the treatment~~.	2. Important Precautions (5) As symptoms such as somnolence and dizziness may occur, caution patients <u>about</u> operating hazardous machine such as driving a car. <u>Patients should also be instructed that, if they experience these symptoms, they should not be engaged in hazardous machine operation, such as driving a car.</u>

[Draft revision] Duloxetine

Add the underlined text and delete the strike-through text

Current version	Draft revision
2. Important Precautions As symptoms such as somnolence and dizziness may occur, caution patients ~~not to engage in~~ hazardous machine	2. Important Precautions As symptoms such as somnolence and dizziness may occur, caution patients <u>about</u> operating hazardous machine, such

~~operation~~, such as driving a car ~~during the treatment~~.	as driving a car. Patients should also be instructed that, if they experience these symptoms, they should not be engaged in hazardous machine operation such as driving a car.

[Draft revision] Venlafaxine

Add the underlined text and delete the strike-through text

Current version	Draft revision
2. Important Precautions (6) As symptoms such as somnolence and dizziness may occur, caution patients ~~not to engage in~~ hazardous machine ~~operation~~ such as driving a car ~~during the treatment~~.	2. Important Precautions (6) As symptoms such as somnolence and dizziness may occur, caution patients about operating hazardous machine such as driving a car. Patients should also be instructed that, if they experience these symptoms, they should not be engaged in hazardous machine operation such as driving a car.

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